Report Documentation Page

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
01 JUN 2014	**N/A**	**-**

4. TITLE AND SUBTITLE	5a. CONTRACT NUMBER
Vasopressin, Sepsis, and Renal PerfusionâA VASST Deficit in Our Understanding*	5b. GRANT NUMBER
	5c. PROGRAM ELEMENT NUMBER
6. AUTHOR(S)	5d. PROJECT NUMBER
Stewart I. J., Sosnov J. A., Chung K. K.,	5e. TASK NUMBER
	5f. WORK UNIT NUMBER
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)	8. PERFORMING ORGANIZATION REPORT NUMBER
United States Army Institute of Surgical Research, JBSA Fort Sam Houston, TX	
9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)	10. SPONSOR/MONITOR'S ACRONYM(S)
	11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION/AVAILABILITY STATEMENT
Approved for public release, distribution unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

15. SUBJECT TERMS

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			
unclassified	**unclassified**	**unclassified**	**UU**	**2**	

Vasopressin, Sepsis, and Renal Perfusion—A VASST Deficit in Our Understanding*

Ian J. Stewart, MD
Jonathan A. Sosnov, MD, MSc
Department of Medicine
San Antonio Military Medical Center
Fort Sam Houston, TX

Kevin K. Chung, MD, FCCM
United States Army Institute of Surgical Research
Fort Sam Houston, TX; and
Uniformed Services University of the Health Sciences
Bethesda, MD

In this issue of *Critical Care Medicine*, Guarido et al (1) present their fascinating work in a model of endotoxemia in rats. Consistent with prior studies, they found that vasopressin could increase blood pressure in animals refractory to phenylephrine. What is provocative about this work is the presumptive mechanism for these findings. In septic animals, this improvement in blood pressure could not be explained by improvements in cardiac function or vasoconstriction from large vessels. The effect appeared to be a result of vasoconstriction within the renal vascular bed as evidenced by decreased renal blood flow (RBF) in vivo and increased renal vascular perfusion pressure in vitro. These effects were attenuated by Y-27632, implying that signaling via the Rho-A/Rho-kinase pathway plays a role. Presumably, this decrease in renal perfusion could potentially result in acute kidney injury (AKI), a syndrome that has been associated with increased mortality in the ICU setting (2). The implication is that in the setting of refractory shock, similar physiology may apply to patients resulting in an increase in AKI with vasopressin.

The current Surviving Sepsis Campaign Guidelines (3), based largely on the results of the VASST trial (4), recommend vasopressin in the setting of refractory shock to either increase mean arterial pressure or decrease the dose of other vasopressors but does not recommend it as a first-line agent. In this study, renal dysfunction was not significantly different between the two groups. However, AKI was defined by the Brussels criteria and not the now commonly used definitions based on relative changes in creatinine and changes in urine output (5–7). A post hoc analysis of the VASST trial (8) using creatinine-based Risk, Injury, Failure, Loss, End-stage renal disease (RIFLE) criteria (5) demonstrated that in patients with RIFLE category 'Risk', vasopressin was associated with a decrease in mortality, decrease in progression to RIFLE 'Injury' and 'Failure', decrease in creatinine, and decrease in the need for renal replacement therapy. Furthermore, other work has found an improvement in urine output (9, 10) and creatinine clearance (10, 11) with vasopressin therapy.

How can these findings be reconciled with the present study? It may simply be the innate differences in humans versus other animals. Alternatively, the degree to which this applies to humans may be smaller, resulting in an insignificant clinical difference. A more intriguing hypothesis, however, is that the findings of Guarido et al (1) do apply to patients. Although RBF and glomerular filtration rate (GFR) are certainly correlated, they are not necessarily the same thing with the later involving a complicated interplay of intrarenal hemodynamics. This is a key insight for interpreting the work by Guarido et al (1). As implied by this study's contrasting findings in control and lipopolysaccharide animals, different disease states may fundamentally change the renal hemodynamic response to vasopressin. Constriction of larger arteries and/or the afferent arteriole would be expected to decrease both RBF and GFR, whereas, conceivably, constriction of the efferent arteriole could decrease RBF and augment GFR. Furthermore, a decrease in medullary blood flow in the setting of preserved cortical blood flow would be expected to decrease RBF and leave GFR relatively unchanged but could result in tubular injury. The literature on the effect of vasopressin on intrarenal hemodynamics is conflicting (12–15). These studies examined different animal models and different diseased and normal states. One explanation for these disparate results is that vasopressin rather than having a static role has subtle, but significant, differences depending on the physiologic setting.

Notably, the VASST trial did not examine a cohort of patients that could be considered a corollary to the refractory shock model reported by Guarido et al (1). Given that the mean arterial blood pressures in both arms at baseline of the VASST trial were approximately 70 mm Hg, vasopressin was examined as a "catecholamine-sparing drug," not necessarily as a therapy for refractory shock. It is possible that vasopressin deleteriously alters renal hemodynamics only in the setting of catecholamine unresponsiveness. This might also help explain the underlying paradox that patients with less severe shock

*See also p. e461.

Key Words: acute kidney injury; renal blood flow; sepsis; shock; vasopressin

Dr. Stewart has disclosed government work. He received support for article research from the United States Air Force. His institution received grant support (Air Force Medical Support Agency [AFMSA] for urinary biomarkers and AFMSA for myoglobin removal using Cytosrob). Dr. Chung has disclosed government work. He and his institution have a patent co-owned with government (burn decision support software). His institution received grant support from the American Burn Association (grant funds to conduct multicenter trial in burn patients with sepsis and acute kidney injury). The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Air Force, the Department of the Army, or the Department of Defense. Dr. Sosnov has disclosed that he does not have any potential conflicts of interest.

DOI: 10.1097/CCM.0000000000000354

(defined by a norepinephrine dose of 15 μg/min or less) had an improved survival with vasopressin in the VASST trial. This hypothesis implies that hemodynamic support for patients in shock may need to be individualized based on severity and etiology. Further human studies will be needed to understand whether the physiology and the Rho-A/Rho-kinase pathway are the same for human beings. Large, prospective human trials are then needed to determine the optimal therapies for patients in various states of shock before clinicians change their practice patterns. Further understanding of renal hemodynamics, and how they differ between disease states, will be vital for guiding future translational research to optimize vasopressin use. Works such as Guarido et al (1) will be vital in the design of these future trials.

REFERENCES

1. Guarido KL, Gonçalves RPM, Gasparotto Júnior A, et al: Increased Activation of the Rho-A/Rho-Kinase Pathway in the Renal Vascular System Is Responsible for the Enhanced Reactivity to Exogenous Vasopressin in Endotoxemic Rats. *Crit Care Med* 2014; 42:e461–e471
2. Ostermann M, Chang RW: Acute kidney injury in the intensive care unit according to RIFLE. *Crit Care Med* 2007; 35:1837–1843; quiz 1852
3. Dellinger RP, Levy MM, Rhodes A, et al; Surviving Sepsis Campaign Guidelines Committee including the Pediatric Subgroup: Surviving sepsis campaign: International guidelines for management of severe sepsis and septic shock: 2012. *Crit Care Med* 2013; 41: 580–637
4. Russell JA, Walley KR, Singer J, et al; VASST Investigators: Vasopressin versus norepinephrine infusion in patients with septic shock. *N Engl J Med* 2008; 358:877–887
5. Bellomo R, Ronco C, Kellum JA, et al; Acute Dialysis Quality Initiative Workgroup: Acute renal failure - definition, outcome measures, animal models, fluid therapy and information technology needs: The Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. *Crit Care* 2004; 8: R204–R212
6. Mehta RL, Kellum JA, Shah SV, et al; Acute Kidney Injury Network: Acute Kidney Injury Network: Report of an initiative to improve outcomes in acute kidney injury. *Crit Care* 2007; 11:R31
7. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group: KDIGO Clinical Practice Guideline for Acute Kidney Injury. *Kidney Inter Suppl* 2012; 2:1–138
8. Gordon AC, Russell JA, Walley KR, et al: The effects of vasopressin on acute kidney injury in septic shock. *Intensive Care Med* 2010; 36:83–91
9. Holmes CL, Walley KR, Chittock DR, et al: The effects of vasopressin on hemodynamics and renal function in severe septic shock: A case series. *Intensive Care Med* 2001; 27:1416–1421
10. Patel BM, Chittock DR, Russell JA, et al: Beneficial effects of short-term vasopressin infusion during severe septic shock. *Anesthesiology* 2002; 96:576–582
11. Lauzier F, Lévy B, Lamarre P, et al: Vasopressin or norepinephrine in early hyperdynamic septic shock: A randomized clinical trial. *Intensive Care Med* 2006; 32:1782–1789
12. Harrison-Bernard LM, Carmines PK: Juxtamedullary microvascular responses to arginine vasopressin in rat kidney. *Am J Physiol* 1994; 267:F249–F256
13. Edwards RM, Trizna W, Kinter LB: Renal microvascular effects of vasopressin and vasopressin antagonists. *Am J Physiol* 1989; 256:F274–F278
14. Correia AG, Denton KM, Evans RG: Effects of activation of vasopressin-V1-receptors on regional kidney blood flow and glomerular arteriole diameters. *J Hypertens* 2001; 19:649–657
15. Cavarape A, Bauer J, Bartoli E, et al: Effects of angiotensin II, arginine vasopressin and tromboxane A2 in renal vascular bed: Role of rho-kinase. *Nephrol Dial Transplant* 2003; 18:1764–1769